REMARKS

The office action dated June 22, 2012 has been carefully considered. By present Amendment, claim 1 is amended to clarify that detecting of the detectable protecting groups is achieved by methods other than immunoassay. Support for this amendment may be found throughout the instant specification by specific illustration, for example paragraphs [0019], [0024], and is implicit in the teaching set forth in paragraph [0007]: "The key advantage is that the methodology is non-destructive and requires no further steps once the final deprotection or detection has been carried out." Since no new matter is added, entry is believed in order and is respectfully solicited. Claims 1-3, 13, and 15-22 remain pending and subject to examination.

35 USC §102

The rejection of claims 1-2, 13, and 15-22 under 35 U.S.C. 102(b) as being anticipated by U.S. Application Pub. No. 2002/045167 to Agris ("Agris") is maintained substantially for reasons of record. Specifically, the Examiner asserts that Agris teaches antibodies specific for oligonucleotide protecting groups applied toward detecting incomplete deprotection on microarrays. According to the Examiner, Agris suggests the antibodies may be used on chips such as developed by Fodor, etc. which are made by synthesizing a plurality of biopolymer species on an array from monomeric or oligomeric nucleotide building blocks comprising detectable protecting groups couple directly to amino groups of the nucleotide building blocks, wherein the detectable protecting groups remain coupled until synthesis of the biopolymer array is complete. The Examiner asserts that Agris figure 8 illustrates steps taken to cleave detectable protecting groups such as Bz and ipr-Pac, with said antibodies, and determine the degree of deprotection by detecting any of Bz and ipr-Pac remaining on an array after cleavage. The Examiner argues that Agris further teaches re-deprotecting until the detectable protecting groups

are no longer detected, indicating that complete deprotection is achieved. According to the Examiner, antibody binding does not destroy the oligonucleotides as required by the instant claims, and Agris purportedly indicates that the method may be used with fluorescent protecting groups such as fluorenylmethoxycarbonyl (Fmoc), and teaches the various protected monomeric building blocks recited in claims 15-22, in paragraphs 0035-0077.

In response the Applicants' previous argument that not all elements are taught, the Examiner contends that the features upon which Applicant relies (i.e., protecting groups detected by methods other than immunoassay) are not recited in the rejected claim(s), and the assertion that immunoassay is impliedly precluded by the functional limitation of "wherein the synthesized biopolymer are not destroyed..." is not persuasive since no objective evidences is set forth establishing that the chip illustrated in figure 8 of Agris has lost utility.

The Examiner argues that contrary to Applicants' insistence that "detectable" should be construed for its ordinary meaning, Applicants interpret the term by operation or functionality (i.e., detection by means other than immunoassay) since Applicants have not amended the actual positive action step of detecting as set forth in the independent claim.

This rejection is traversed and reconsideration is respectfully requested.

Independent claim 1 is directed to a quality control method for achieving complete deprotection of protected reactive groups in on-chip synthesis of a biopolymer array, the method comprising (a) synthesizing a plurality of biopolymer species on an array from monomeric or oligomeric nucleotide building blocks comprising detectable protecting groups coupled directly to amino groups of the nucleotide building blocks, wherein the detectable protecting groups remain coupled until synthesis of the biopolymer array is complete, and wherein the detectable protecting groups are selected from fluorescent groups, radioactively protectable groups,

electrochemically protectable groups, and UV or IR protecting groups; (b) taking one or more steps to cleave the detectable protecting groups, (c) determining a degree of deprotection by detecting any of the detectable protecting groups remaining on the array after cleavage, said detecting being achieved by methods other than immunoassay, and (d) repeating steps (b) and (c) until the detectable protecting groups are no longer detected, indicating that complete deprotection is achieved, wherein the quality control method is performed entirely on-chip and wherein the synthesized biopolymer are not destroyed by practice of the quality control method.

Applicants note that all detection methods described and illustrated by Agris are based on immunoassay. Detection by immunoassay requires treating the synthesized array/chip with antibody and subjecting the chip to incubation conditions, detection solutions and cleaning solutions, and therefore usability of the chip is impacted even if immunoassay theoretically does not require destruction of intended functionality of the chip.

In contrast, the instant methods involve detection of protecting groups by methods other than immunoassay, by detection of a detectable feature of the protecting group, not by post-synthesis addition of a detectable moiety to a protecting group which is thereafter detected. By limiting detection methods to non-immunoassay methods, processing relating to quality control of deprotection is reduced. Further, background signal common to antibody-based detection protocols caused by non-specifically binding antibody can only be eliminated by washing, a step not necessary where immunoassay is not employed.

Agris is directed to an allegedly novel antibody that binds to a synthesized oligo having a protecting group bound thereto. The bound antibody is detectible by immunoassay. Presence of signal indicates that antibody is bound and deprotection is not complete. A step of incubating the synthesized chip with antibody is therefore required prior to a determination of de-protection.

According to the instant claims, on the other hand, the synthesized chip is synthesized with the protecting groups already detectable. They do not have to be rendered detectable in an additional processing step. Further, no additional processing or washing is necessary prior to undertaking any additional deprotection steps which may be determined as required in accordance with the quality control methods.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). All methods for detecting incomplete deprotection of a synthetic oligo disclosed by Agris are by immunoassay (paragraph [0083]). The methods of Agris rely on rendering a protecting group detectable by addition of an antibody. In contrast, the instant claims determine deprotection by methods involving detection of protection groups which are detectable on the synthesized oligo without further processing. The invention of Agris is mutually exclusive with the instant claims, and Agris does not suggest or motivate production of synthesized oligos using detectable protecting groups which enable the instant quality control methods.

Claims 1-2, 13, and 15-22 are therefore novel and patentable under 35 U.S.C. 102(b) over Agris. Reconsideration is respectfully requested.

35 USC §103

Claims 1-2, 13, 15-22, and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agris in view of Nagaich et al (1989 Nucleic Acids Research 17:5125-5134).

Agris is relied on as set forth above. The Examiner notes that Agris does not teach stilbene protecting groups, such as set forth in claim 3. Nagaich is applied for teaching stilbene protecting groups (elected species) for cytidine, adenine and guanine nucleosides as recited in instant claim 3. The Examiner concludes that it would be obvious to utilize the stilbene protecting groups of Nagaich in making microarrays and conducting the analysis of deprotection thereof as disclosed by Agris.

This rejection is traversed and reconsideration is respectfully requested.

As noted above, Agris fails to suggest or motivate the production of synthetic oligos with detectable protecting groups, or quality control methods which ensure complete deprotection without reliance on immunoassay. Agris teaches post-synthetic modification of any existing protecting groups by incubation with an antibody which binds to organic protecting groups bound to a nucleotide, and not otherwise. The present claims, on the other hand, do not rely on immunoassay and rely on protecting groups which have been rendered detectable by, for example, some signal-generating label so that any protecting groups remaining on the oligo/ array are readily detected by the corresponding non-immunoassay detecting technology.

Nagaich teaches stilbene, one of the protecting groups of the instant methods. However Agris modified in view of Nagaich does not suggest the subject matter of the instant claims; rather it suggests development and/or implementation of an antibody in accordance with Agris which detects stilbene when bound to a synthesized oligonucleotide. Nagaich fails to overcome the deficiencies of the primary reference with respect to failure to teach or suggest all limitations of the independent claim. Dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious. *Hartness Int'l, Inc. v. Simplimatic Eng'g Co.*, 819 F.2d 1100, 1108, 2 USPQ2d 1826, 1831 (Fed. Cir. 1987).

Claims 1-3, 13 and 15-22 are therefore nonobvious and patentable under 35 U.S.C. 103(a) over Agris in view of Nagaich. Reconsideration is respectfully requested.

Conclusion.

Applicants submit that the foregoing is a comprehensive and persuasive response to the outstanding rejections set forth in the Office Action dated June 22, 2012. If, however, the Examiner perceives any remaining issues which may be readily resolved thereby, he is urged to contact Applicants through their attorney listed below. Otherwise reconsideration and allowance are earnestly solicited.

Sincerely,

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